REMARKS

By the present communication, claims 47-55 are amended. No new matter has been added. Support for the amended claims can be found throughout the application as filed, including, but not limited to, p. 31, line 8 and p. 31, line 34. Upon entry of the present amendment, claims 47-56 will be pending and under examination. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim Objections

In the Office Action, claims 47-55 are objected to for reciting "SEQ ID NO." instead of "SEQ ID NO:". The claims have been amended to correct this matter of form. Applicants request withdrawal of this objection.

In the Office Action, claims 47-55 are objected to for reciting "a modified, full-length recombinant human arginase I …, which is covalently linked to at least one polyethylene glycol (PEG) molecule." The claims have been amended as requested by the Examiner to recite "a modified, full-length recombinant human arginase I …, wherein said human arginase I is covalently linked to at least one polyethylene glycol (PEG) molecule." Applicants request withdrawal of this objection.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

In the Office Action, claims 47-56 stand rejected under 35 U.S.C.§ 112, first paragraph, because the specification allegedly does not enable the full scope of the claims, *i.e.,* a method of treating a human liver, breast, or colon cancer by administering a recombinant, modified human arginase I polypeptide. However, the Office acknowledges that the specification is enabling for a method of treating a human rectal cancer comprising administering to the subject a pegylated recombinant human arginase I of SEQ ID NO: 9. (Office Action, p. 3). Applicants respectfully traverse the rejection.

The first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed

invention without "undue experimentation." *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (*citing In re Wands*, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988)). Some experimentation, even a considerable amount, is not "undue" "if it is merely routine, or if the specification . . . provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* In light of the reasons that follow, the specification provides sufficient direction to a skilled artisan for treating a human liver, breast, or colon cancer. Accordingly, the full scope of the claimed invention is enabled.

The working examples of the present application unambiguously disclose that a recombinant, modified arginase I polypeptide treats liver, breast, and colon cancer, as evidenced by the treatment of tumors in animal xenograft models and in a human patient. The experimental support in the application for the treatment of each malignancy is summarized below.

Liver Malignancy: Support for the treatment of liver malignancy is found in the specification as filed at least at Example 15 (see generally, p. 29, lines 3-20, and Fig. 24); Example 16 (see generally, p. 29, line 21-41 and Figs. 25A and 25B); and Example 17 (see generally, p.30, lines 1-17 and Figs. 26A and 26B). In these Examples, three different human hepatoma cell lines (Hep3B2.1-7, PLC/PRF/5, and HuH-7, respectively) were implanted subcutaneously into the back of BALB/c nude mice. In each case, treatment with pegylated arginase slowed the growth of the tumor.

Breast Malignancy: Support for the treatment of breast malignancy is found in the specification as filed at least at Example 18 (see generally, p. 30, line 18-43 and Fig. 27). In this Example, a human breast cancer cell line (MCF-7) was implanted subcutaneously into the back of BALB/c nude mice. After treatment with pegylated arginase, the tumor disappeared entirely from the mice within 20 days from the start of the experiment.

Colon/Rectal Malignancy: Support for the treatment of colon/rectal malignancies is found in the specification as filed at least at Example 12 (see generally, p. 27, line 30 to p. 28, line 13, and Figs. 21, 28, and 29). In this Example, a patient with metastatic rectal carcinoma

was treated with pegylated recombinant arginase. Both biochemical and radiological improvement of the disease was observed.

It is important to note that although Example 12 describes the treatment of a rectal malignancy, both rectal and colon malignancies affect the intestinal tract, and differ only in the portion of the large intestine where the tumor is located. The National Cancer Institute refers to these cancers collectively as "colorectal cancers" and notes that the cells lining the inside of the colon and rectum are similar. *See*, *e.g.,* http://www.cancer.gov/cancertopics/types/colon-and-rectal. Consequently, the cancers that arise in this part of the digestive system are related. Based on the similarity between of colon and rectal cancers, one of skill in the art would predict that treatments that affect rectal malignancies could be adapted to colon cancer without undue experimentation.

With regard to the animal xenograft studies demonstrating treatment of liver and breast malignancies, Applicants also respectfully remind the Office human clinical data is not required to support utility or enablement. *See* MPEP § 2107.03. The evidence needed to show that a claimed method is enabled can take a variety of forms. For example, animal studies, in an art-recognized animal model, will generally be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. *Id.* The subcutaneous xenograft tumor models used in the examples are the standard for cancer drug screening in the pharmaceutical industry. The U.S. Food and Drug Administration considers a drug's effectiveness against xenografts sufficient for clinical trial approval. *See* Sausville and Burger, *Cancer Res* 2006; 66: (7). April 1, 2006 (a copy of which is enclosed for the convenience of the Examiner). In short, human clinical trials are not required to show enablement of the claimed methods.

Collectively, the data in the application demonstrate enablement that is commensurate in scope with the claims. The studies discussed above confirm that those of ordinary skill in the art would expect that a modified, full-length recombinant human arginase I polypeptide can be successfully used to treat human liver, breast, colon or rectal malignancies. Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 103(a)

In the Office Action, claims 47-56 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Tepic *et al.* (WO 09/06421), Vockley *et al.* (U.S. 6,316,199, herein "Vockley"), in view of Clark *et al.* (WO 02/44360, herein "Clark") and Mehvar *et al.* (*J Pharm Pharmaceut Sci* 3(1): 125-136, 2000, herein "Mehvar"). Applicants respectfully traverse the rejection.

As an initial and fundamental task, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (*citing In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). However, while the Supreme Court suggested a flexible approach to obviousness determinations, it also emphasized that an invention "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (2007). The fact that references can be combined is insufficient to establish obviousness if one of ordinary skill in the art would not have reasonably predicted that the combination would result in success. *KSR* at 1396. Furthermore, the Court warned the fact finder to be aware of the distortion caused by hindsight bias and to be cautious of arguments based upon *ex post* reasoning. *Id.* at 1397.

The cited references fail to teach or suggest a method of treating a human liver, breast, colon or rectal malignancies by administering a modified, full-length recombinant human arginase I polypeptide In fact, for the reasons detailed below, a careful reading of the references would suggest to one of ordinary skill in the art that Arginase I would <u>not</u> be effective for the treatment of liver, breast, colon or rectal cancer. As such, a <u>*prime facie*</u> case of obviousness cannot be established.

A. The Office acknowledges that the treatment of cancer is unpredictable.

The fact that the references can be combined is insufficient to establish obviousness if one of ordinary skill in the art could not reasonably predict the result of that combination. In this case, Applicants submit that the cited references do not provide any reasonable basis to predict that administering a modified, full-length recombinant human Arginase I to a patient could treat a human liver, breast, colon or rectal malignancy. The Office has acknowledged that the treatment of cancer is unpredictable, stating

> The liver, breast, rectal, or colon cancers are very diverse in terms of organ, tissue , and genetic disorders, or chemical or environmental effect and mode of cancer development, which cause said cancers are different from each other, and treating the cancers of liver, breast or colon is unpredictable…

(Office Action, p. 4).

The instant claims are directed the treatment of human liver, breast, colon, or rectal malignancies using Arginase I. Cancer is an umbrella term and tumors vary from those that are benign to those that are so virulent that all therapy is useless. Accordingly, treatments for cancer are normally tailored to the particular type of cancer present. Various types of cancer have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy. Despite the unpredictability in the art, Applicants have clearly shown that modified, recombinant Arginase I is useful in the treatment of specific cancers—namely, human liver, breast, colon or rectal malignancy. Of particular importance, the application demonstrates powerful anti-cancer activity for the claimed compositions.

Due to the unpredictability in cancer treatments known in the art, the instant claims could not have been predicted from the teachings of the prior art with a reasonable expectation of success. The primary reference, Tepic, discloses an extracorporeal method using an arginine-degrading enzyme during dialysis to reduce the arginine level in an animal. Tepic fails to teach or suggest *parenteral* administration of an arginine-degrading enzyme to treat cancer, as recited in the instant claims. Although Tepic states that arginine decomposing enzymes could be used, "it must be accompanied by dialysis in order to remove ammonia." (Tepic, p. 8, lines 20-22). Nowhere does Tepic teach or suggest that parenteral administration of modified arginase I could be used to treat human liver, breast, colon or rectal cancer. Given the unpredictability in the art noted by the Examiner, one of skill in the art could not expect to treat liver, breast, colon or rectal cancer using modified arginase I based on the teachings of Tepic, alone or in combination with the other references.

B. Vockley teaches away from the administration of Arginase I polypeptides for the treatment of cancer.

The unpredictability in the art is further shown by a careful reading of Vockley. Vockley teaches away from administering either Arginase I or Arginase II polypeptides for the treatment of cancer. In Example 8, Vockley measured the arginase activity in solid tumor samples and normal adjacent tissues (col. 41, lines 21-39). The investigators found that arginase activity was increased in the cells of breast, ovarian, lung, colon, testicular, and prostate tumors. Vockley further measured the serum arginase activity in a number of different cancer patients. They found that arginase activity is present at high levels in the sera of metastatic cancer patients (*See* Table 2). According to Vockley,

> All of these data suggest that arginase expression and activity may be a key factor in the formation and metastasis of cancer. As arginase depletes the arginine concentration within the cell, it shuts down nitric oxide synthesis disabling tumor-infiltrating macrophage and limiting the cytotoxic effect of nitric oxide. At the same time, polyamine synthesis may be stimulated by the production of large amounts of ornithine, the end product of the arginase reaction, through ornithine decarboxylase, while proline biosynthesis is enhanced through the action of ornithine aminotransferase on the excess ornithine. The effect of elevated arginase activity in the serum is to have a systemic interference with the immune system to include inhibiting lymphocytes and three different splenic derived killer cells. Combined, there is a stimulation of cancer growth while at the same time a local and systemic inhibition of the immune system.

(col. 42, lines 21-36, emphasis added). This passage makes clear that increased arginase activity and depletion of arginine in cancer cells and in the serum may lead to the progression of disease. It follows from Vockley that the administration of either Arginase I or Arginase II would not be indicated for the treatment of cancer because the level of arginase is already elevated in these patients. Thus, one of skill in the art would expect that administration of arginase to cancer patients would have significant detrimental effects.

The inconsistent teachings between Tepic and Vockley cannot support a *prima facie* case of obviousness. One of skill in the art would not have modified the method taught by Tepic to

use the recombinant Arginase I of Vockley because the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. (MPEP § 2143.01). A prior art reference teaching disadvantages that lead away from the claimed invention must impact the obviousness analysis. *See U.S. v. Adams*, 383 U.S. 39, 52 (1966). Because Vockley teaches that arginase activity and depletion of arginine in cancer cells and in the serum may lead to the progression of disease, one of skill in the art would not have a reason to modify or combine the references in the way alleged by the Office. As such, a *prima facie* case of obviousness cannot be established.

C. Clark and Mehvar do not overcome the deficiencies of the primary references..

Applicants submit that the additional secondary references cited by the Office in no way overcome the essential deficiency or unpredictability in the primary references discussed above. First, the Office relies on Clark for teaching a modified arginine deiminase for treating cancer including sarcomas, hepatomas, and melanomas. (Office Action, p. 8). Applicants respectfully submit that one of skill in the art would not have been motivated to substitute arginine deiminase as described in Clark for human arginase I as described in Vockley for the treatment of cancer. There is no recognition in the art that a modified human arginase I would be as useful as arginine deiminase in eliciting an equivalent therapeutic response. As described in MPEP 2144.06, "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." In fact, the art suggests that these two proteins are not equivalent and would not be interchangeable for the treatment of cancer.

Arginine deiminase (EC 3.5.3.6) is an enzyme that catalyzes the chemical reaction

$$\text{L-arginine} + H_2O \leftrightarrow \text{L-citrulline} + NH_3$$

Thus, the two substrates of this enzyme are L-arginine and H_2O, whereas its two products are L-citrulline and NH_3. On the other hand, arginase I converts L-arginine into L-ornithine and urea. Given the different products of the reactions catalyzed by these enzymes, it is clear that these two

enzymes are not equivalent, and it cannot be predicted with a reasonable expectation of success which enzymes have sufficient *in vivo* activity to be effective for the treatment of human liver, breast, colon or rectal cancer. Simply because arginine deiminase was effective in treating a human liver cancer does not mean that one could reasonably predict that a different enzyme—an arginase—could also be used to treat a liver cancer or any other cancers. The effectiveness of treatments using one enzyme is not in any way an assurance of the effectiveness of another enzyme.

Mehvar is relied on for teaching a PEG-modified arginase protein, but this reference does not teach or suggest a method of administering a PEG-modified, full-length recombinant human arginase I to a patient for the treatment of a human liver, breast, colon or rectal malignancy. Accordingly, the Clark and Mehvar references cannot cure the fundamental defect in either the Tepic or Vockley references mentioned above, and a *prima facie* case of obviousness cannot be established.

D. Conclusion.

As discussed above, the methods of the invention relate to administering a PEG-modified, full-length recombinant human arginase I to a patient for the treatment of a human liver, breast, colon or rectal malignancy. Tepic required dialysis to achieve a therapeutic effect and Vockley suggested that administering arginase to treat cancer would not be effective. These deficiencies are not remedied by Clark and Mehvar. As such, the combined references fail establish a *prima facie* case of obviousness for the claimed methods. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 103.

* * * *

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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